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Relationship of stroke and bleeding risk profiles to efficacy and safety of dabigatran dual therapy versus warfarin triple therapy in atrial fibrillation after PCI: An ancillary analysis from the RE-DUAL PCI trial

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Abstract

Background In the RE-DUAL PCI trial of patients with atrial fibrillation (AF) who underwent percutaneous coronary intervention (PCI), dabigatran dual therapy (110 or 150 mg bid, plus clopidogrel or ticagrelor) reduced International Society on Thrombosis and Haemostasis bleeding events compared with warfarin triple therapy, with noninferiority in overall thromboembolic events. This analysis assessed outcomes in relation to patient bleeding and stroke risk profiles, based on the modified HAS-BLED and CHA_2DS_2-VASc scores.

Methods The primary endpoint, major bleeding event (MBE) or clinically relevant nonmajor bleeding event (CRNMBE), was compared across study arms in patients categorized by modified HAS-BLED score 0-2 or ≥3. The composite endpoint of death, thromboembolic event, and unplanned revascularization rates was compared in patients categorized by CHA_2DS_2-VASc score 0-1, 2, or ≥3.

Results Risk of MBE or CRNMBE was lower with dabigatran dual therapy (both doses) versus warfarin triple therapy, irrespective of modified HAS-BLED category (treatment-by-subgroup interaction *P*-value 0.584 and 0.273 for dabigatran 110 and 150 mg dual therapy, respectively, vs warfarin). Risk of the composite thromboembolic endpoint was similar across CHA_2DS_2-VASc categories and consistent with overall study results (interaction *P*-value 0.748 and 0.075 for dabigatran 110 and 150 mg dual therapy, respectively, vs warfarin). Higher HAS-BLED scores were associated with higher risks of bleeding in AF patients after PCI in a treatment-independent analysis.

Conclusion Dabigatran dual therapy reduced bleeding events irrespective of bleeding risk category and demonstrated similar efficacy regardless of stroke risk category when compared with warfarin triple therapy.

Highlights

- RE-DUAL PCI compared dabigatran dual therapy vs warfarin in AF post-PCI
- This analysis assessed RE-DUAL outcomes relative to bleeding and stroke risk score
- Dabigatran dual therapy reduced bleeding vs warfarin irrespective of HAS-BLED score
- Dabigatran dual therapy had similar efficacy to warfarin across CHA_2DS_2-VASc scores

Introduction

Stroke prevention is a cornerstone of management in patients with atrial fibrillation (AF).[1] Many patients with AF have associated coronary artery disease, which may require percutaneous coronary intervention (PCI) with stenting.[2,3] In such patients, the need for oral anticoagulation (OAC) for prevention of thromboembolism and antiplatelet therapy for prevention of stent thrombosis and coronary events has to be balanced against the risk of serious bleeding from combined OAC and antiplatelet therapy.[2,4,5] Traditionally, these patients have been managed by triple therapy, consisting of a vitamin K antagonist (VKA) plus dual antiplatelet therapy with aspirin and clopidogrel.[2,5-9] Observational studies, randomized trials, and meta-analyses have more recently suggested that dual antithrombotic treatment, consisting of a VKA combined with 1 antiplatelet agent, reduces bleeding events without increased risk of thromboembolic events when compared with triple therapy.[10-14] Consistent with this, a focused update from the European Society of Cardiology on dual antiplatelet therapy in coronary artery disease concluded that the risk of bleeding associated with triple therapy increases in proportion to its duration, and recommended that the duration of therapy should be minimized, dependent on bleeding and ischemic risks.[15] A 2018-dated North American Expert Consensus recommended a dual-therapy regimen (OAC plus single antiplatelet therapy with 1 $P2Y_{12}$ inhibitor) as the default strategy for most patients with AF who underwent PCI.[5]

The landscape of OAC use in patients with AF has been altered by the availability of non-VKA OACs (NOACs).[16,17] NOACs provide superior or equal safety and similar efficacy, and are more convenient to use than VKAs.[18-22] The North American Expert Consensus, mentioned above,[5] provides a recommendation to use a NOAC over a VKA in patients with AF who underwent PCI. The NOAC, rivaroxaban, in combination with clopidogrel or ticagrelor was compared in a randomized trial against VKAs plus dual antiplatelet therapy in PIONEER-AF, an exploratory randomized trial in patients with AF

who underwent PCI.[23] PIONEER-AF found that reduced-dose (15 mg daily) dual therapy or a very low-dose rivaroxaban-based triple therapy strategy decreased rates of "clinically significant" bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention) compared with VKAs plus dual antiplatelet therapy, but the study was underpowered to demonstrate greater stroke prevention in patients with AF[22] and the rivaroxaban dose strategies used were not those recommended for AF stroke prevention.

The RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; NCT 02164864) randomized 2725 PCI patients with AF to treatment with the direct thrombin inhibitor, dabigatran, dual therapy in combination with clopidogrel or ticagrelor, or to triple therapy consisting of warfarin in combination with clopidogrel or ticagrelor and aspirin.[24,25] The dabigatran doses investigated (110 or 150 mg bid) are those approved worldwide for the prevention of stroke in AF.[19,26]

The primary endpoint of RE-DUAL PCI was International Society on Thrombosis and Haemostasis major bleeding events (MBE) or clinically relevant nonmajor bleeding events (CRNMBE) during follow-up (mean duration: 14 months). The incidence of the primary endpoint was 15.4% in the dabigatran 110 mg dual therapy group versus 26.9% in the warfarin triple therapy group (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.42-0.63; $P < 0.001$ for noninferiority; $P < 0.001$ for superiority), and 20.2% in the dabigatran 150 mg dual therapy group versus 25.7% in the corresponding warfarin triple therapy group, which excluded elderly patients outside the United States (HR: 0.72; 95% CI: 0.58-0.88; $P < 0.001$ for noninferiority; $P = 0.002$ for superiority). The RE-DUAL PCI trial also tested for the noninferiority of dabigatran dual therapy (both dabigatran doses combined) compared with warfarin triple therapy in the

composite endpoint of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization. The incidence of this composite endpoint was 13.7% in the combined dabigatran dual therapy groups versus 13.4% in the warfarin triple therapy group (HR: 1.04; 95% CI: 0.84-1.29; *P* = 0.005 for noninferiority).

The RE-DUAL PCI trial included patients with a range of bleeding and stroke risks, categorized respectively by the modified HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess)[27] and the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category)[28] scales. This prespecified ancillary analysis of the RE-DUAL trial assessed safety and efficacy outcomes in relation to patient baseline bleeding and stroke risk profiles, based on these clinical risk scores.

Methods

The primary endpoint in this analysis (MBE or CRNMBE) was compared in the 3 study arms of the RE-DUAL PCI trial in relation to modified HAS-BLED score categories 0-2 or ≥3 (low and high risk, respectively). The modification to the HAS-BLED score omitted only the stable international normalized ratio (INR) component, as multiple INR measurements were not collected at baseline. Thromboembolic events were compared in relation to CHA_2DS_2-VASc score categories 0-1, 2, or ≥3 (low, moderate, and high risk, respectively).

Statistical analyses

Clinical characteristics are summarized by modified HAS-BLED and CHA_2DS_2-VASc scores categories, categoric variables are reported as frequencies and percentages, and continuous variables as means and standard deviations. For comparison of treatment groups with regard to the primary and composite thromboembolic endpoints within the modified HAS-BLED and CHA_2DS_2-VASc subgroups, respectively, stratified Cox proportional hazard regression models, including age group (nonelderly or elderly [<70 or ≥70 years old in Japan and <80 or ≥80 years old everywhere else]) as a stratifying factor and treatment arm (dabigatran 110 mg dual therapy vs warfarin triple therapy; dabigatran 150 mg dual therapy and dabigatran 110 mg dual therapy combined vs warfarin triple therapy), were applied. For the dabigatran 150 mg dual therapy versus warfarin triple therapy comparison, unstratified models were applied (excluding elderly patients outside the United States in the warfarin triple therapy group). Corresponding HRs and 2-sided 95% Wald CIs for HRs were calculated for the modified HAS-BLED and CHA_2DS_2-VASc subgroups. In addition, exploratory treatment-by-subgroup interaction *P*-values are provided. Furthermore, a treatment-independent stratified Cox proportional hazard regression analysis was performed including HAS-BLED and CHA_2DS_2-VASc subgroup, respectively, as the only factor in the model.

Results

Patients

The clinical characteristics of patients and their therapies at baseline (including antiplatelet therapy and antacid medication) are shown in Table I according to bleeding and stroke risk categories. Over half of the patients had a modified HAS-BLED score ≥3 and a CHA_2DS_2-VASc score ≥3 (Table II).

As expected, older patients and those with more prevalent comorbidities had higher modified HAS-BLED and CHA_2DS_2-VASc scores. The most common access site was the radial site (63.5% of patients overall). Clopidogrel was the most frequently used $P2Y_{12}$ inhibitor at baseline (in >80% of patients), and tended to be prescribed more frequently in patients with higher HAS-BLED and CHA_2DS_2-VASc scores. While similar proportions of patients were prescribed proton pump inhibitors (PPIs) between HAS-BLED groups, more patients appeared to be treated with PPIs in the higher CHA_2DS_2-VASc score groups.

Mean (SD) modified HAS-BLED scores were 2.7 (0.7) and 2.8 (0.7) in the dabigatran 110 mg dual therapy versus warfarin triple therapy groups, and 2.6 (0.7) and 2.7 (0.8) in the dabigatran 150 mg dual therapy versus warfarin triple therapy groups. Mean (SD) CHA_2DS_2-VASc scores were 3.7 (1.6), 3.8 (1.5), 3.3 (1.5), and 3.6 (1.5) in the respective groups. Of the 981 patients randomized to warfarin triple therapy, 804 were treated and had valid INR measurements more than 90 days after randomization. In these 804 patients, the mean percentage of time in the guideline-defined target INR range was not relevantly different across the modified HAS-BLED and CHA_2DS_2-VASc score subgroups (Table III).

	Total	Modified HAS-BLED		CHA_2DS_2-VASc score		
	N = 2725	0-2 (n = 943)	≥3 (n = 1782)	0-1 (n = 203)	2 (n = 467)	≥3 (n = 2055)
Mean age, y (SD)	70.8 (8.7)	64.3 (8.8)	74.2 (6.3)	60.4 (7.3)	65.5 (7.5)	73.0 (7.7)
Age group, n (%)						
Elderly*	458 (16.8)	64 (6.8)	394 (22.1)	0 (0)	17 (3.6)	441 (21.5)
Nonelderly	2267 (83.2)	879 (93.2)	1388 (77.9)	203 (100)	450 (96.4)	1614 (78.5)
Male sex, n (%)	2070 (76.0)	777 (82.4)	1293 (72.6)	198 (97.5)	436 (93.4)	1436 (69.9)
Diabetes mellitus, n (%)†	993 (36.4)	285 (30.2)	708 (39.7)	13 (6.4)	65 (13.9)	915 (44.5)
Mean baseline creatinine clearance, mL/min (SD)	78.0 (29.8)	92. 7 (33.8)	70.3 (24.1)	103.7 (31.5)	92.3 (31.2)	72.2 (26.6)
Previous MI, n (%)	699 (25.7)	251 (26.6)	448 (25.1)	12 (5.9)	59 (12.6)	628 (30.6)
Previous CAD, n (%)†	1828 (67.1)	593 (62.9)	1235 (69.3)	105 (51.7)	269 (57.6)	1454 (70.8)
Previous PCI, n (%)†	912 (33.5)	285 (30.2)	627 (35.2)	38 (18.7)	115 (24.6)	759 (36.9)
Previous CABG, n (%)†	287 (10.5)	72 (7.6)	215 (12.1)	9 (4.4)	26 (5.6)	252 (12.3)
Previous stent thrombosis, n (%)‡	68 (2.5)	28 (3.0)	40 (2.2)	2 (1.0)	11 (2.4)	55 (2.7)

Previous PE, n (%)[§]	36 (1.3)	8 (0.8)	28 (1.6)	0 (0)	2 (0.4)	34 (1.7)
Previous stroke, n (%)[†]	226 (8.3)	6 (0.6)	220 (12.3)	0 (0)	2 (0.4)	224 (10.9)
Previous SE, n (%)[†]	21 (0.8)	3 (0.3)	18 (1.0)	0 (0)	0 (0)	21 (1.0)
Previous stroke/TIA, n (%)[†]	317 (11.6)	25 (2.7)	292 (16.4)	0 (0)	2 (0.4)	315 (15.3)
Type of AF, n (%)[†]						
Persistent	484 (17.8)	169 (17.9)	315 (17.7)	37 (18.2)	93 (19.9)	354 (17.2)
Permanent	888 (32.6)	284 (30.1)	604 (33.9)	45 (22.2)	128 (27.4)	715 (34.8)
Paroxysmal	1351 (49.6)	488 (51.7)	863 (48.4)	119 (58.6)	246 (52.7)	986 (48.0)
Indication for PCI, n (%)						
Stable angina or positive stress test	1182 (43.4)	392 (41.6)	790 (44.3)	81 (39.9)	213 (45.6)	888 (43.2)
ACS	1375 (50.5)	490 (52.0)	885 (49.7)	113 (55.7)	220 (47.1)	1042 (50.7)
Staged procedure	462 (17.0)	155 (16.4)	307 (17.2)	37 (18.2)	70 (15.0)	355 (17.3)
Other	170 (6.2)	63 (6.7)	107 (6.0)	12 (5.9)	34 (7.3)	124 (6.0)
Type of stent, n (%)[‖]						
BMS	404 (14.8)	143 (15.2)	261 (14.6)	21 (10.3)	71 (15.2)	312 (15.2)

DES	2251 (82.6)	766 (81.2)	1485 (83.3)	176 (86.7)	383 (82.0)	1692 (82.3)
DES and BMS	41 (1.5)	18 (1.9)	23 (1.3)	4 (2.0)	7 (1.5)	30 (1.5)
Other	21 (0.8)	13 (1.4)	8 (0.4)	1 (0.5)	6 (1.3)	14 (0.7)
Access site, n (%)[††]						
Radial	1731 (63.5)	623 (66.1)	1108 (62.2)	133 (65.5)	326 (69.8)	1272 (61.9)
Femoral	972 (35.7)	308 (32.7)	664 (37.3)	65 (32.0)	138 (29.6)	769 (37.4)
Antiplatelet medications at baseline, n (%)	2693 (98.8)	915 (97.0)	1778 (99.8)	198 (97.5)	459 (98.3)	2036 (99.1)
Clopidogrel	2363 (86.7)	787 (83.5)	1576 (88.4)	171 (84.2)	398 (85.2)	1794 (87.3)
Ticagrelor	327 (12.0)	131 (13.9)	196 (11.0)	34 (16.7)	61 (13.1)	232 (11.3)
Antacid medications at baseline	1739 (63.8)	601 (63.7)	1138 (63.9)	118 (58.1)	286 (61.2)	1335 (65.0)
PPI	1641 (60.2)	564 (59.8)	1077 (60.4)	110 (54.2)	272 (58.2)	1259 (61.3)
H2 blocker	140 (5.1)	51 (5.4)	89 (5.0)	12 (5.9)	20 (4.3)	108 (5.3)
Other	41 (1.5)	17 (1.8)	24 (1.3)	5 (2.5)	6 (1.3)	30 (1.5)

ACS, acute coronary syndrome; *AF*, atrial fibrillation; *BMS*, bare-metal stent; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CHA_2DS_2-VASc,* Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65-74 years, Sex category; *DES*, drug-eluting stent; *HAS-BLED,* Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *PE*, pulmonary embolism; *PPI*, proton pump inhibitors; *SD*, standard deviation; *SE*, systemic embolism; *TIA*, transient ischemic attack.

* Elderly: patients aged ≥80 years old (≥70 years old in Japan). † Data missing from 1 patient (1 in the HAS-BLED 0-2, and in the CHA_2DS_2-VASc 0-1 group). ‡ Data missing from 44 patients (18 and 26 as well as 4, 12, and 28 patients in the HAS-BLED 0-2, HAS-BLED ≥3, CHA_2DS_2-VASc 0-1, CHA_2DS_2-VASc 2, and CHA_2DS_2-VASc ≥3 groups, respectively). § Data missing from 8 patients (4 and 4 as well as 1, 1, and 6 patients in the HAS-BLED 0-2, HAS-BLED ≥3, CHA_2DS_2-VASc 0-1, CHA_2DS_2-VASc 2, and CHA_2DS_2-VASc ≥3 groups, respectively). || Data missing from 8 patients (3 and 5, as well as 1 and 7, in the HAS-BLED 0-2, HAS-BLED ≥3, CHA_2DS_2-VASc 0-1, and CHA_2DS_2-VASc ≥3 groups, respectively). †† Data missing from 22 patients (12 and 10 as well as 5, 3, and 14 patients in the HAS-BLED 0-2, HAS-BLED ≥3, CHA_2DS_2-VASc 0-1, CHA_2DS_2-VASc 2, and CHA_2DS_2-VASc ≥3 groups, respectively).

Table I

Clinical characteristics in relation to modified HAS-BLED and CHA_2DS_2-VASc scores

	CHA_2DS_2-VASc score, n (%)		
Modified HAS-BLED score, n (%)	0-1	2	≥3
0-2	196 (7.2)	313 (11.5)	434 (15.9)
≥3	7 (0.3)	154 (5.7)	1621 (59.5)

CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65-74 years, Sex category; *HAS-BLED,* Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess.

Table II

Patients categorized by both modified HAS-BLED and CHA_2DS_2-VASc scores

HAS-BLED or CHA_2DS_2-VASc score		N	Percentage of time in the guideline-defined target INR range, mean (SD)*
HAS-BLED score			
	0-2	241	62.0 (25.0)
	≥3	563	65.0 (23.5)
CHA_2DS_2-VASc score			
	0-1	47	62.6 (25.9)
	2	113	62.5 (23.4)
	≥3	644	64.5 (24.0)

CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65-74 years, Sex category; *HAS-BLED,* Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess; INR, international normalized ratio.

***** Treated set. Excludes INR data from the first 90 days. Guideline-defined target INR is 2.0-3.0. For Japanese patients ≥70 years old the target range is 2.0-2.6.

Table III

Percentage of time in the guideline-defined target INR range for the warfarin triple therapy group according to modified HAS-BLED or CHA_2DS_2-VASc score category

Bleeding events: primary endpoint

The primary endpoint (MBE or CRNMBE) was more frequent in patients in HAS-BLED category ≥3 versus 0-2 in the treatment-independent Cox regression analysis (HR 1.41; 95% CI 1.17-1.71) (Figure 1A).

Risk of bleeding events was lower with dabigatran dual therapy (each dabigatran dose) versus warfarin triple therapy, irrespective of the HAS-BLED category (Figure 2). Treatment-by-subgroup interaction *P*-values were 0.584 and 0.273, respectively, for the dabigatran 110 mg dual therapy versus warfarin triple therapy and dabigatran 150 mg dual therapy versus warfarin triple therapy comparisons.

Risks of bleeding events in patients categorized by baseline thromboembolic risk are reported in Supplementary Figure 1A.

Composite thromboembolic endpoint

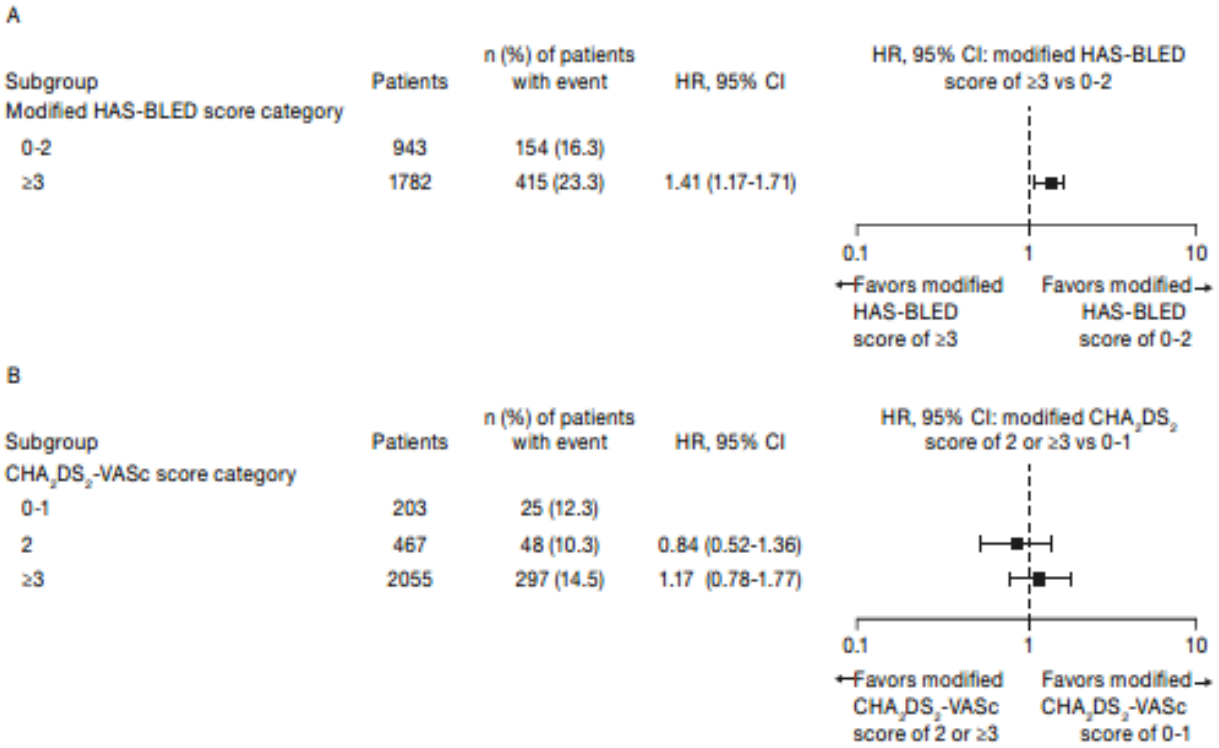
HRs for the composite thromboembolic endpoint of death, thromboembolic event, and unplanned revascularization were 0.84 (95% CI 0.52-1.36) and 1.17 (95% CI 0.78-1.77) for CHA_2DS_2-VASc categories 2 and ≥3, respectively, versus category 0-1 in the treatment-independent Cox regression analysis (Figure 1B).

There was no consistent trend for the composite thromboembolic endpoint across the dabigatran dose groups: interaction *P*-values were 0.739 for the dabigatran 110 mg dual therapy versus warfarin triple therapy comparison and 0.075 for the dabigatran 150 mg dual therapy versus warfarin triple therapy comparison (Figure 3). For the endpoint of definite stent thrombosis by CHA_2DS_2-VASc score, interaction *P*-values were 0.990 for the dabigatran 110 mg dual

therapy versus warfarin triple therapy comparison and 0.928 for the dabigatran 150 mg dual therapy versus warfarin triple therapy comparison (Supplementary Figure 2A). The number of patients with stent thrombosis is generally small, so that interpretation should be done carefully.

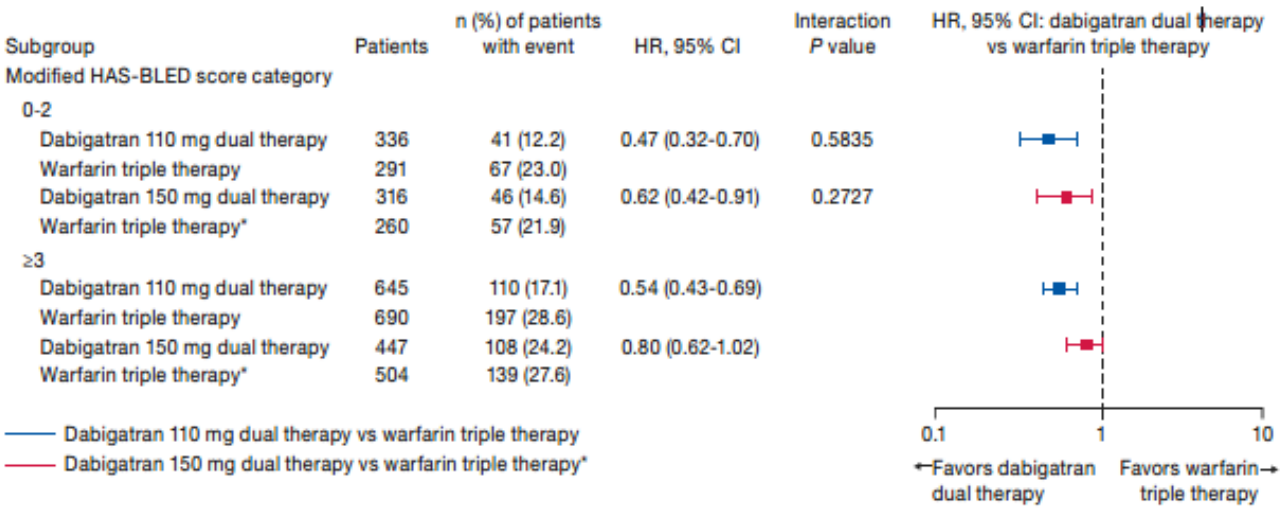
A further analysis was performed to assess thromboembolic events in patients categorized into CHA_2DS_2-Vasc 0-2, 3-4, and 5+ score groups. No interaction was observed for the dabigatran 110 mg dual therapy versus warfarin triple therapy comparison (interaction *P*-value 0.748). The comparison of the dabigatran 150 mg dual therapy versus warfarin triple therapy resulted in an interaction *P*-value of 0.062 (Supplementary Table I).

Risks of composite thromboembolic events in patients categorized by baseline bleeding risk are reported in Supplementary Figure 1B. For the outcome of definite stent thrombosis by HAS-BLED score, results are displayed in Supplementary Figure 2B. Interpretation of the outcome of definite stent thrombosis by treatment group is hindered by the limited number of events.



CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65-74 years, Sex category; *CI*, confidence interval; *CRNMBE*, clinically relevant nonmajor bleeding event; *HAS-BLED,* Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess; *HR,* hazard ratio; *ISTH*, International Society on Thrombosis and Haemostasis; *MBE*, major bleeding event. HRs and 95% CIs from a treatment-independent Cox-proportional hazard model stratified by age (elderly vs nonelderly).

Figure 1. Treatment-independent Cox regression analysis (A) ISTH MBEs or CRNMBEs by modified HAS-BLED score. (B) Death, thromboembolic events, or unplanned revascularization by CHA_2DS_2-VASc score.



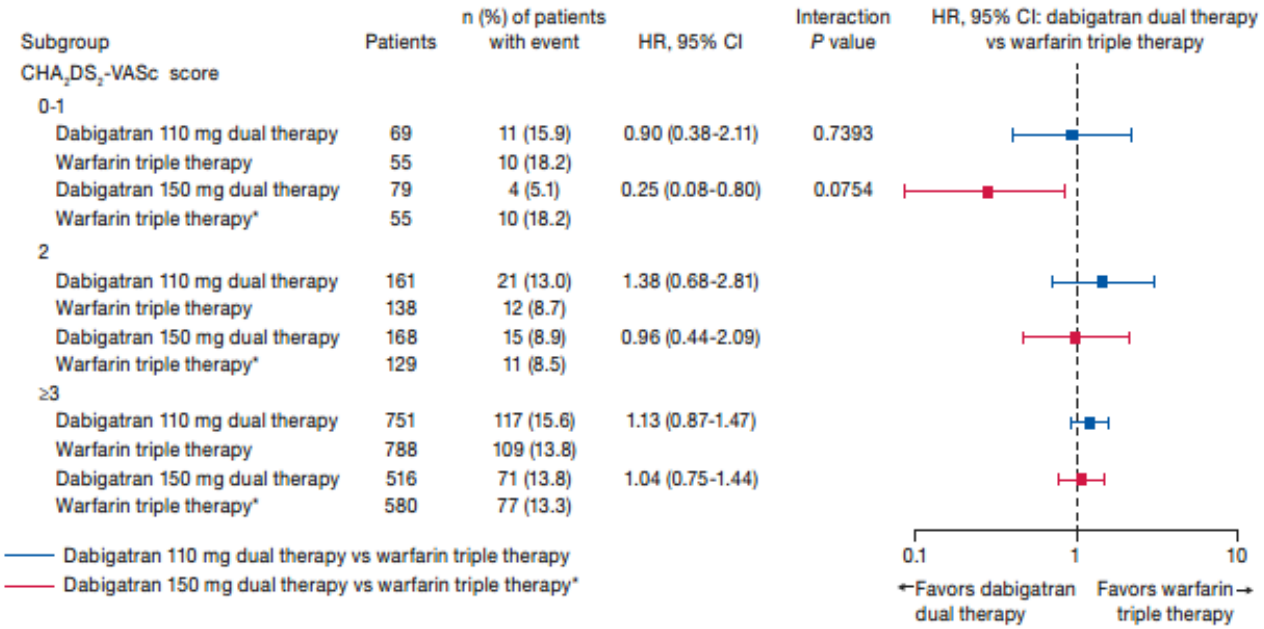
CI, confidence interval; *CRNMBE*, clinically relevant nonmajor bleeding event; *HAS-BLED*, Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly age/frailty, Drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs, or alcohol excess; *HR,* hazard ratio; *ISTH*, International Society on Thrombosis and Haemostasis; *MBE*, major bleeding event.

* For the comparison with dabigatran 150 mg dual therapy, patients aged ≥80 years (≥70 years in Japan) outside the United States are excluded.

Interaction *P* values for treatment and modified HAS-BLED score subgroups.

HRs and 95% CIs from a Cox-proportional hazard model; stratified by age (elderly vs nonelderly) for dabigatran 110 mg dual therapy versus warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy versus warfarin triple therapy.

Figure 2. ISTH MBEs or CRNMBEs by modified HAS-BLED score.



CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65-74 years, Sex category; *CI*, confidence interval; *HR*, hazard ratio.

* For the comparison with dabigatran 150 mg dual therapy, patients aged ≥80 years (≥70 years in Japan) outside the United States are excluded.

Interaction *P* values for treatment and CHA_2DS_2-VASc score subgroups.

HRs and 95% CIs from a Cox-proportional hazard model; stratified by age (elderly vs nonelderly) for dabigatran 110 mg dual therapy versus warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy versus warfarin triple therapy.

Figure 3. Death, thromboembolic events, or unplanned revascularization by CHA_2DS_2-VASc score.

Discussion

In this analysis from the RE-DUAL PCI trial, the principal finding was that the risk of the primary bleeding endpoint (MBE or CRNMBE) was lower for dabigatran dual therapy (each dabigatran dose) than warfarin triple therapy, irrespective of the modified HAS-BLED category (0-2 or ≥3). Second, the risk of the composite thromboembolic endpoint was similar across CHA_2DS_2-VASc categories (0-1, 2, and ≥3) and consistent with the overall study results for both doses of dabigatran dual therapy versus warfarin triple therapy comparisons. [24]

It is reassuring that, irrespective of bleeding risk, dabigatran dual therapy was associated with lower risks of MBEs or CRNMBEs compared with warfarin triple therapy in a setting where antiplatelet therapy is needed. Nevertheless, the appropriate use of a bleeding risk score, such as modified HAS-BLED, is to draw attention to the modifiable bleeding risk factors and to identify those patients at high risk, to schedule early review and follow-up. Thus, the use of the modified HAS-BLED score in patients with AF presenting with an acute coronary syndrome or undergoing PCI may help decision making in this respect. Of note, recent analyses have shown that simply focusing on modifiable bleeding risk factors alone is an inferior strategy compared with formal bleeding risk assessment using the modified HAS-BLED score in predicting serious bleeding events.[29-31] It is noteworthy that, in treatment-independent analysis, the risks of MBEs or CRNMBEs were 41% higher in patients who had modified HAS-BLED scores ≥3 (the majority of patients in our study) compared with patients who had a lower modified HAS-BLED score (0-2). A high CHA_2DS_2-VASc score has been reported to be predictive of thromboembolic outcomes in patients with AF undergoing PCI.[32] No consistent trend in the composite thromboembolic endpoint could be observed for CHA_2DS_2-VASc scores in our treatment-independent analysis. Nevertheless, the CHA_2DS_2-VASc score was designed for the prediction of stroke in AF, but given that it represents a cluster of common cardiovascular risk factors, there is unsurprisingly a relationship to cardiac events.

These findings support the view that higher modified HAS-BLED scores do identify higher risk patients—and for these, the absolute treatment benefits (regardless of type of OAC treatment) may be greater. The findings also lend support to the new North American expert consensus, which recommends that a dual therapy approach should be the "default strategy" for most patients.[5] In both the North American and European statements, risk stratification is recommended to help choose appropriate therapies, where absolute event rates could play a role.[5,15]

In relation to the doses of dabigatran dual therapy, rates of MBE/CRNMBE were similar for the 110 mg and 150 mg bid doses (12.2% and 14.6%, respectively) in patients with a HAS-BLED score 0-2, and were lower for the 110 mg than 150 mg dose (17.1% and 24.2%, respectively) in patients with a HAS-BLED score ≥3. This indicates that the choice of dabigatran 110 mg dual therapy is reasonable in patients with AF who are at very high bleeding risk post-PCI, e.g., the very elderly, consistent with the European prescribing information for dabigatran.[33]

A limitation of our study is that, as in any subgroup analysis, it is not powered for formal statistical analyses within each modified HAS-BLED and CHA_2DS_2-VASc score category. Therefore, these results should be regarded as exploratory and interpreted with caution. Additionally, a modified HAS-BLED score was applied due to the lack of multiple INR measurements at baseline. Because of the limited numbers of events, we have not focused on components of the composite thromboembolic endpoint, nor have we subdivided endpoints further by HAS-BLED and CHA_2DS_2-VASc score categories. Nevertheless, we were able to analyze prospectively collected and adjudicated outcomes in the largest published trial of OACs in the setting of patients with AF who underwent PCI/stenting. The present ancillary analysis does not address the issue of drug dosing, although no significant interaction was observed for dosing in relation

to stroke and bleeding strata. In the main RE-DUAL PCI trial, where dabigatran 110 mg was used as part of dual therapy compared to warfarin, there were numerically higher but not significant differences in thromboembolic outcomes, but these comparisons were grossly underpowered.

In conclusion, dabigatran dual therapy (110 or 150 mg) reduced bleeding events compared with warfarin triple therapy, irrespective of bleeding risk, when assessed by modified HAS-BLED score. In addition, the risk of thromboembolic events was similar between dabigatran dual therapy and warfarin triple therapy, regardless of CHA_2DS_2-VASc scores.

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Conflict of interest

Gregory Y. H. Lip has served as a consultant for Bayer/Janssen, Bristol-Meyers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo. No fees are directly received personally.

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Availability of data and material

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link:
https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html
All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Submission of declaration

This article has not been published previously and is not under consideration for publication elsewhere. Its publication is approved by all the authors.

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